Exhibit B

For

Response to Office Action, Paper No. 12
Docket No. 299002032400
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B

SHUSAKU YAMAMOTO

(Translation)

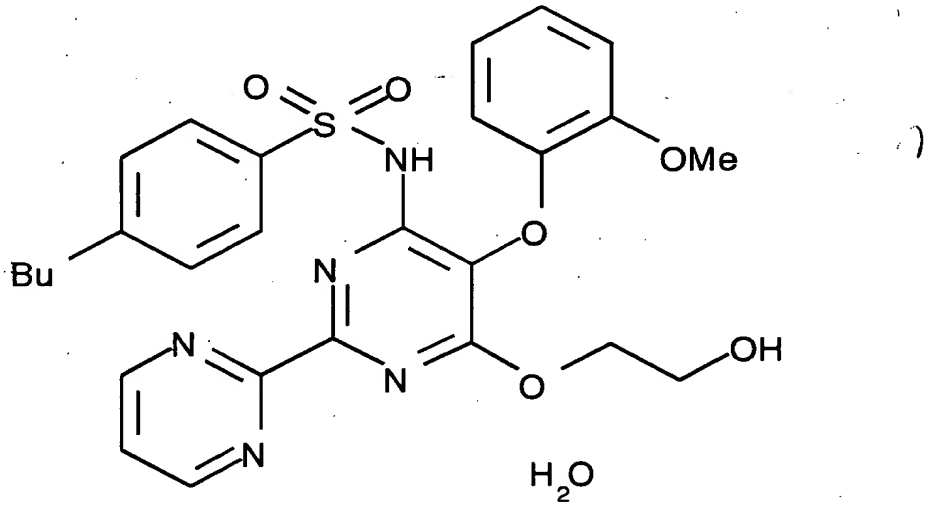
14923

Registration:1994/04/01 Update:2002/12/27

bosentan

Roche

bosentan; RO-47-0203*; RO-47-0203/029; Tracleer(R)



$C_{27}H_{29}N_5O_6S \cdot H_2O$:569.64

p-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(o-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]benzenesulfonamide monohydrate

Pharmacology: Endothelin ETA antagonist, endothelin ETB antagonist

Efficacy: Agents for circulatory organs (others)(219.99), hypotensives (214.00), agents for respiratory organs (others)(229.00), dermatologic agents (others)(269.90)

ATC C1D, C2A2, D11A, R7X, L1X9, N7X
CAS 157212-55-0, 147536-97-8
PAT EP 526708, EP 713875, JP 93 222003, US 4292740, WO 97 9318
Highest Stage Released

[Development in Japan]

[Pharmaceutical classification] Development stage
developer / indication / dosage form / trade name [seller] / orphan drug status
stage history

[New effective component] Phase I
Actelion Japan/ pulmonary hypertension/ / /
stage history Phase I 2001/12 (registration: 2001/12/04 update: 2001/12/04)

[New efficacy] Preparing for clinical study
Actelion Japan/ chronic heart failure/ / /
stage history (registration: 2001/12/04 update: 2001/12/04)

[New effective component] Preclinical study (discontinuation)
Chugai/ cerebrovascular contraction after subarachnoid hemorrhage, renal ischemia/ oral drug/ /
stage history preclinical study 1994/04, preclinical study (discontinuation) 2000/09 (registration: 1994/04/01 update: 2002/10/01)

[Development Overseas]

registration: 1994/12/01 update: 2002/11/20

dosage form : tablet, IV injection

Indications

country development stage/ developer/ trade name [seller]

Congestive heart failure

AU Phase III/ Actelion, Genentech/ Tracleer[Actelion]

CH Phase III(Suspended)/ Roche/ Tracleer

CH Phase III/ Actelion/ Tracleer

GB Preclinical(Suspended)/ Roche/

US Phase III/ Actelion, Genentech/ Tracleer[Actelion]

Subarachnoid hemorrhage

CH Phase I(Suspended)/ Roche/

Inflammatory enteropathy

CA Preclinical(Suspended)/ Roche/

Scleroderma

CH Clinical/ Actelion/ Tracleer

Metastatic melanoma

CH Preparation for Clinical/ Actelion/

Idiopathic fibroid lung

CH Phase II/ Actelion/

Pulmonary hypertension

AU Pre-registration/ Actelion/ Tracleer

CA Launched/ Actelion/ Tracleer[Actelion]
CH Launched/ Actelion/ Tracleer
EU Launched/ Actelion/ Tracleer
US Launched/ Actelion, Genentech/ Tracleer[Actelion]

Essential hypertension
CH Phase II(Suspended)/ Roche/

[Outline]

Summary

Bosentan is a nonpeptide antagonist of endothelin ETA and ETB receptors.

Bosentan had been developed overseas to be adapted for subarachnoid hemorrhage, congestive heart failure (Marketletter 1997/12/01), hypertension and inflammatory enteropathy. However, in PhaseIII study (REACH-1), it was observed that administration of bosentan led to a dose-related increase in transaminases. The development was therefore discontinued.

Thereafter, Actelion (Switzerland) resumed development of bosentan to be adapted for chronic congestive heart failure.

In a 16-week PhaseIII study for treatment of pulmonary hypertension, walk distance was increased by 11% in the bosentan 125mg/day group and by 16% in the 250mg/day group (The Pink Sheet 2001/08/13, p24).

In a PhaseIII study of severe chronic heart failure patients, two primary end points were not achieved.

For the treatment of pulmonary hypertension, bosentan tablet was applied in USA on November 17, 2000, were given orphan drug status on December in the same year, and were approved on November 20, 2001 (The Pink Sheet 2001/11/26, p4). In Europe, the bosentan tablet was also given orphan drug status (Scrip 2001/03/07, p24), was applied in 2001 (Pharma Marketletter 2001/09/24, p18), and was approved on May, 2002.

For the treatment of child pulmonary hypertension or pulmonary hypertension, combined therapy with epoprostenol has also been

studied (The Pink Sheet 2001/08/20, p11). For treatment of scleroderma (Pharma Marketletter 2002/04/01, p28), idiopathic fibroid lung and metastatic melanoma, bosentan has also been studied (Pharma Marketletter 2002/06/10, p25).

In the study of 122 scleroderma patients who had experienced digital ulcers, bosentan significantly suppressed the occurrence of new digital ulcers (Scrip 2002/08/21, p22).

In Japan, initially, Japan Roche (presently Chugai Phermaceutical Co., Ltd.) had been developing bosentan for the treatment of cerebrovascular contraction after subarachnoid hemorrhage and renal ischemia (Mix 1996/03). Thereafter, Actelion Phermaceuticals Japan started developing bosentan for the treatment of pulmonary hypertension by utilizing bridging study. In the Subcommittee on Pharmaceutical Affairs on December 26, 2002, bosentan was approved in orphan drug status in indication for pulmonary arterial hypertension.

Further, bosentan has been under development for the treatment of chronic heart failure (Nikkan Yakugyo 2001/11/30).

Market & Partnership

Bosentan was licensed to Actelion on November 5, 1998.

On December 14, 2000, Actelion amd Genentech signed an agreement for the joint development and sale in the United States of bosentan in the treatment of heart failure. Under the terms of the agreement, Genentech had to reach the primary end point of PhaseIII study for the treatment of heart failure in order to exercise the co-marketing and promotion option. However, Genentech were not successful and did not exercise the option.

In the United States, four companies became distributors (The Pink Sheet 2001/12/10, p26).

Overseas, bosentan is expected to appear on the market indicated for heart failure on the first half of 2003 (Nikkei Sangyo 2000/10/20). In the United States, bosentan came onto the market in indication of pulmonary hypertension on December, 2001. In the same indication, bosentan came onto the market in Germany on June, 2002 (Pharma Marketletter 2002/06/10, p28).

In Japan, bosentan is expected to appear on the market indicated for pulmonary hypertension within 2003 (Nikkan Yakugyo 2001/11/30).

[Abstracts for Development in Japan]

[New effective component]

Other publications

<Preclinical studies>

·Endothelin receptor antagonist - bosentan suppresses mucosal disorders in rat acute gastic mucosal disorder models- / Abstracts of 68th Meeting of Japanese Pharmacological Society : No.S36-5, March 1995, Nagoya.

[Abstracts for Overseas Development]

Nonclinical Studies

Bosentan competitively blocked ET-1 inducing constriction of removed rat aorta (ETA) and sarafotoxin S6c(ETB) inducing

constriction of rat trachea, pA2 was 7.2 and 6.0, respectively. *In vivo*, po administration of 1-30 mg/kg of bosentan to rats and iv administration of 0.3-100 mg/kg of bosentan to rats suppressed increases in blood pressure due to a large amount of ET-1, showing a long duration. Bosentan had no influence on BP[1].

In rat mesenteric endothelium exposed artery, 10^{-7}~10^{-5} M bosentan suppressed both phases of endothelin-1 (ET-1) inducing biphasic vascular constriction in a concentration-dependent manner. FR-139317, which is a ETA receptor-specific antagonist, had influence only on the second phase. 10^{-5} M bosentan suppressed ET-3-inducing relaxation of intact endothelium artery constricted with norepinephrine by 1/2 to maximum. FR-139317 having an equal concentration did not suppress it. In the renal artery of old age SHR (Spontaneous Hypertension Rat), ET-1 inducing constriction was antagonized by 10^{-5} M bosentan, but not by FR-139317[2].

In another experiment using removed rat hearts, bosentan improved the left ventricle pressure, LVdP/dtmax, myocardial ischemia, and the recovery of coronary bloodstream after reperfusion. Endothelium-dependent vasodilation reaction at the time of completion of ischemia/reperfusion was held in bosentan-treated hearts, but not in solvent-treated control hearts. The size of LV infarction was significantly reduced in the bosentan-treated hearts as compared to the solvent-treated hearts[3]. Bosentan clearly had a protection action for damage to the myocardial muscle in pig myocardial ischemia/reperfusion models, thereby improving bloodflow to reperfusion regions[4]. In rat myocardial ischemia/edema models, bosentan was more effective for suppression of ST elevation and albumin diapedesis than ETA specific antagonist FR-139317[5].

po administration of 100 mg/kg/day of bosentan and ip

administration of L-arginine 250 mg/kg/day of reduced the SBP of cyclosporine-inducing hypertension rat to the level of normal blood pressure rats. L-arginine also reduced the BP of normal blood pressure rats, but bosentan had no influence on BP[6].

When bosentan (100 mg/kg/day) was administered to DOCA-salt hypertensive rats for 6 weeks, BP was not substantially reduced, but hypercardia and circumvascular/subendocardial fibrosis were significantly reduced ($p<0.05$ in each case with respect to a non-administration group). Enalapril(3 mg/kg/day) had no effect on BP and circumvascular fibrosis, but significantly reduced subendocardial fibrosis as compared to the non-administration group ($p<0.05$). Mibefradil (30 mg/kg/day) significantly reduced BP ($p<0.001$), and substantially suppressed cardinal remodeling due to hypertension[7].

In SHR and DOCA-salt hypertension rats which tend to have cerebral stroke, bosentan reduced BP. Bosentan also reduced peripheral vascular resistance and LV hypertrophy[8].

In eight anesthetized renal hypertensive dogs, iv bolus administration of 3 mg/kg of bosentan + iv infusion of 7 mg/kg/hr of bosentan increased plasma ET-1 concentration by a factor of 30 as compared to before the administration ($p=0.0001$). In this model, bosentan significantly reduced LV constriction-phase pressure, average aorta pressure (AOP), LVEDP and left atrium pressure. Average AOP was reduced in normal pressure dogs administered with bosentan, but the magnitude of the reduction was small ($p=0.0002$ with respect to hypertension dogs)[9].

When four cumulative doses of bosentan were administered to anesthetized dogs (0.1 mg/kg bolus administration + 0.23 mg/kg/hr 30-minute infusion, 0.3 mg/kg + 0.7 mg/kg/hr, 1 mg/kg +

2.33 mg/kg/hr, 3 mg/kg + 7 mg/kg/hr), BP was decreased in a dose-dependent manner. In non-anesthetized dogs, bosentan (0.3 mg/kg+0.7 mg/kg/hr, 3 mg/kg+7 mg/kg/hr) similarly reduced AOP in the constriction phase and in the extension phase in a dose-dependent manner. Bosentan is believed to effectively control renal hypertension by peripheral vasodilation[10].

In rat coronary artery-ligated chronic heart failure models and sham operated controls, 100 mg/kg of bosentan persistently decreased MAP. When 100 mg/kg of bosentan was used in conjunction with 10 mg/kg of cilazapril, MAP was more significantly reduced than when any one of them was solely administered[11].

When 10 mg/kg of bosentan was administered to chronic heart failure dogs, LVEDP was significantly reduced as compared to before the administration, and LVdP/dt and the LV internal diameter reduction rate were significantly increased[12].

100 mg/kg/day of bosentan was po administered to male Wistar rats having streptozotocin-inducing diabetes for 5-6 weeks. As a result, motor nerve conduction rate was improved as compared to untreated diabetic rats (39.7 vs 36.6 m/sec), however, it was still lower than the value (42.7 m/sec) of non-diabetic rats. The sciatic nerve conduction rate of untreated diabetic rats was 49% of that of non-diabetic rats. The sciatic nerve conduction rate of bosentan-administered rats was 75% of that of non-diabetic rats. Bosentan significantly suppressed endothelin-1 inducing hypotension and tachycardia in diabetic rats, but subsequent hypertension was not influenced. The iv administration of 10 mg/kg of bosentan led to a transient increase in nerve Doppler speed and arterial pressure and a transient decrease in HR both in non-diabetic rats and diabetic rats[13].

In ulcerative rats experimentally altered by intrarectal injection of trinitrobenzene sulfonic acid, pretreatment with bosentan (10-60 mg/kg, po) and administration of bosentan once a day for 5 days suppressed a colon injury score and myeloperoxidase activity in a dose-dependent manner. This effect was significant when administration was performed at a dose of 30 and 60 mg/kg ($p \leq 0.05$ with respect to controls). When bosentan was administered after induction of colitis, a dose of 60 mg/kg had a significant protective effect ($p \leq 0.05$ with respect to controls)[14].

Clinical studies

In a randomized, double-blind, parallel study with 57 mild to moderate hypertension patients, 2000 mg of bosentan and 20 mg of enalapril was orally administered once, DBP was significantly reduced as compared to before the administration ($p<0.01$ and $p<0.001$). Bosentan had substantially no influence on SBP, although HR ($p<0.01$) and the ET-1 level were significantly increased. No change was found in the aldosterone value and the PRA value[15].

In a randomized, double-blind, placebo-controlled study with 32 severe pulmonary hypertension patients, bosentan was orally administered for at least 12 weeks and effectiveness and safety were evaluated. The bosentan regimen was 62.5 mg/administration (twice a day) for 4 weeks and then 125 mg/administration. Exercise capacity was the primary end point of the study. The 6-minute walk distance was improved up to 70 m after 12 weeks in the bosentan group as compared to the baseline. The distance was decreased by 6 m in the placebo group (the difference was 76 m, $p=0.021$). This improvement was maintained for at least 20 weeks. The cardiac index was further increased by 1.0 $l/min/m^2$ in the bosentan group than in the placebo group ($p<0.0001$). The pulmonary vascular resistance was decreased by 223 $dyn \cdot s/cm^5$ in the bosentan

group, and was increased by 191 dyn·s/cm^5 in the placebo group (the difference was -415, p=0.0002). In the bosentan group, the Borg index level was decreased and the WHO functional class was improved. Three patients who discontinued the study due to clinical deterioration were all in the placebo group (p=0.033). No difference was found in the number and types of adverse events between both groups[16].

A BREATHE-1 study which was a placebo-controlled, double-blind study for bosentan was conducted for pulmonary hypertension in WHO classes III, IV. Among the registered cases, 85 cases in 13 facilities were analyzed for heart function using an echocardiographic and Doppler method. 84% of the cases had primary pulmonary hypertension. Placebo was administered to 29 cases, while 62.5 mg or 125 mg of bosentan was administered twice a day to 56 cases. A 6-minute walk test and an echocardiac test were conducted before administration and 16 weeks after administration. No difference in clinical symptoms, hemodynamics, and heart function measured by echocardiography before administration was found between the bosentan group and the placebo group. After 16 weeks, the bosentan group extended the walk distance by 37 m as compared to the placebo group (p=0.036), improved the temporal integrated value of the instantaneous bloodstream rates at the mitral valve inlet and the left ventricle outlet and increased the cardiac index by 0.4 l/min/m^2 (p=0.007)[17].

Bosentan (100 mg once a day, 500 mg once a day, 1000 mg once a day, and 1000mg twice a day), enalapril (20 mg once a day), or placebo was orally administered for average 25.9-27.6 days to 293 mild to moderate essential hypertension patients. In the bosentan 500, 2000 mg/day groups and the enalapril group, DBP while the patient was sitting was significantly decreased as compared to the placebo group. Moreover, in the bosentan 500, 1000,

2000 mg/day groups and the enalapril group, SBP while the patient was sitting was significantly decreased as compared to the placebo group[18].

1 g/day of bosentan was orally administered for 2 weeks to 6 patients with congestive heart failure who had received standard therapy using an ACE inhibitor, a diuretic and a digoxin. In this case, decreases in PCWP, RAP and BP and increases in CI and SVI were found as compared to before administration. Tolerance to bosentan was satisfactory and no change in HR was found. Improvement was increased in day 14 than in day 1. This was considered to be attributed to the combination of the ACE inhibitor, the digoxin and the diuretic[19),20]. In a randomized, double-blind study with 24 congestive heart failure (CHF) patients, placebo or bosentan was administered (100 mg, 15 min iv infusion → after 60 min, 200 mg, 15 min iv infusion). Bosentan significantly decreased MAP, SVR, PCWP and right atrium pressure and significantly increased the cardiac index. HR was not influenced[21].

Literature

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